REMARKS

Attached to this Preliminary Amendment is a Declaration Under 37CFR§1.132 which is being filed to present test data which show the criticality of the particular polymeric excipients that are recited in the claims of the present application with regard to the formation of granulations of the present.

The present invention deals with pharmaceutical compositions wherein the peculiar choice of the binders used for their preparation plays an essential role in imparting the desired properties to the final pharmaceutical compositions.

In fact the granulates as described in the present application can be used in various forms for preparing the final pharmaceutical composition since they can be simply pout in a sachet and administered to a patient in such form or can be compressed in a tablet form to provide a final dosage form.

The Declaration provides data which shows that the choice of the binders is essential since some binders do not allow an acceptable granulation of the claimed active ingredients to be formed and others do not impart sufficient flow properties or will form granules which are too hard for further convenient processing. In addition, the test data show that granulates produced using all of the binders recited in the claims have good dispersability in water, but in particular, polyethylene glycol 400 and propylene glycol produce dispersible granulations which have a good appearance which makes these binders particularly suitable for the preparation of pharmaceutical compositions in sachet form. These results were not predictable from the prior art.

Claims 1-7 were rejected under 35 U.S.C. 102(b) as being anticipated by Silver, EP 588 539A (hereinafter

Silver). This rejection is in error for the following reasons.

The present invention is a pharmaceutical composition containing as active ingredients both Vitamin D and a calcium salt (see Claim 1 at lines 1 and 2). The Silver patent was cited as disclosing a pharmaceutical composition having at least ingredients (a), (b) and (c) and optionally the component which is selected from lactose, sorbitol and calcium phosphate (see Claim 6, page 5). Silver only refers to active derivatives of Vitamin D 2 and Vitamin D3 (See Claim 1) and never mention Vitamins D2 and D3 as such, those who are skilled in the art appreciate the important differences (in terms of chemical structure, physico-chemical properties and activity) between the natural Vitamins D2and D3 (which are the subject of the present application) and teir derivatives as described and claimed in the Silver patent. For this reason, Silver does not teach anything that would solve the problem confronted by the present applicants.

Silver does not disclose the use of a calcium salt as an active ingredient. The only use of a calcium salt according to Silver is as an optional excipient or carrier.

Moreover, calcium phosphate is disclosed by Silver only as an excipient that is added in order to make a solid composition that is specifically defined in Claim 1 as ``an amount sufficient to impart the characteristics of a solid to the composition.'' The use of polyethylene glycol 400 as a binder and the ratio of 1-2 g of calcium salt to 500-1000 IU vitamin D, is disclosed in the Silver patent.

Silver is only concerned with a ratio of Vitamin D to calcium salt to the extent that it has an impact on the excipient properties of the calcium salt.

There is nothing of record that would suggest the addition of the binders recited in claim 1 to any

composition described by Silver. Therefore, based on the reasons listed above and the differing composition of vitamins and their derivatives, the present claimed invention is not anticipated by Silver.

Claims 1-8 and 13-18 have been rejected under 35 U.S.C. 103(a) as being unpatentable over FR-A-2 724 844 (hereinafter FR `844). The FR `844 patent is limited to a particular pharmaceutical composition that does not include calcium phosphate (See examples 1-9, pages 3 and 8-10). The particular composition must be prepared in a ``humid environment'' (see claim 1 and more specifically claim 4, page 11). However, because of the specifically chosen binders of the present invention, the application can be prepared without using water. Further, it is well known in the art that the use of a humid process of preparation can leave traces of humidity in the granules, which may result in a degradation of the Vitamin D, which undergoes spontaneous oxidation.

The present invention requires the use of calcium salts and their analogues, i.e. compounds that have a high content of calcium but are insoluble. The calcium salts used in the prior art have been processed by using a granulation process that avoids forming granules having poor flow characteristics. This made them unsuitable for processing using ordinary high output machines. However, when used in suspensions, these granules increased the rate of sedimentation causing a ``sand effect'', thereby decreasing the uniformity of the distribution of the active ingredients within the product which adversely affects the rate of patient compliance with a prescribed dosing schedule. In order to make pharmaceutical compositions for oral use that do not present a ``sand effect'' it is necessary to identify the exact additives that show acceptable texture, and at the same time allow for an industrial preparation of the composition. Therefore, it was necessary to utilize binders that would be effective in a dry environment, with high

concentrations of an insoluble calcium salt such as calcium phosphates. These conditions and binders are not disclosed in FR `844.

The binding agents of the present invention, propylene glycol, polyethylene glycol, liquid paraffin or silicone oil are not disclosed in FR `844. More particularly with respect to FR `844, the formulation contains 500 mg of calcium (see page 10, line 5). In examples 2, 4, 5, and 6 of the FR `844 patent the following quantities are reported respectively: 1.250g of calcium carbonate (0.5g of calcium ion); 1.5g of calcium pidolate (0.2g of calcium ion); 2g of calcium pidolate (0.27g of calcium ion); and 1.250g of calcium carbonate (0.5g of calcium ion). Furthermore, in Examples 3, 8 and 9, 3.74g of calcium pidolate are present containing 0.5g of calcium ion and example 7 reports 2.72g of calcium pidolate containing 0.35g of calcium ion.

Claim 1 of FR `844 specifically requires the use of a dry and wet binder, the process comprising the formation of solutions and suspensions. On page 6, line 31, it is reported that the wet granulation of calcium carbonate is mixed with polyvinyl pyrrolidone (a solid) to obtain a humid mass which is dried on an air bed (see page 7, lines 8 and 9). Other solid binders (e.g. cellulose, maltodextrines, sweeteners) may be used. However, the binders of the present invention rely on the use of liquid binders and a homogenizing step. Therefore, the claimed compositions are not made obvious by the FR `844 patent. It is apparent from the foregoing that it is insufficient to have a simple combination of Vitamin D and calcium in a pharmaceutical formulation. It is the unique ratio of Vitamin D and calcium together with propylene glycol, polyethylene glycol, liquid paraffin or silicone oil binders that result in significant advantages over the prior art. The present invention provides homogeneous distribution low dosages of Vitamin D with high dosages of calcium that is stable, bioavailable, palatable and

suitable for high-speed production machines. Additionally, the present formulation overcomes problems due to ``granulation'' of the calcium salt. The glycol diffuses over the calcium granules, resulting in a binding effect over the small granules of coated Vitamin D_3, resulting in a mixture having flow characteristics conducive to processing by high output machines and actually facilitates subsequent reconstitution of a dispersion.

To fully appreciate the inventiveness of the claimed invention, it should be kept in mind that the present invention resulted from efforts to solve the problem of formulating a calcium salt which is a fine powder with a Vitamin D_3 which is not a powdered material in such a manner that the formulation is a granular blend that is dispersible in water, has an acceptable taste and has a good appearance. The attached Declaration reports that not all of the binders form a composition which has suitable properties that make the formulation acceptable as a dispersible granulation. For these reason, it is believed that the prior art fails to make obvious the compositions and methods as defined by the amended claims.

An early and favorable action is earnestly solicited.

Respectfully submitted,

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